

- (a) Randomization.
- (b) Blinding.
- 6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).
- 6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- 6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.
- 6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- 6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.
- 6.4.9 The identification of any data to be recorded directly on the CRF's (i.e., no prior written or electronic record of data), and to be considered to be source data.
- 6.5 *Selection and Withdrawal of Subjects*
- 6.5.1 Subject inclusion criteria.
- 6.5.2 Subject exclusion criteria.
- 6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:
 - (a) When and how to withdraw subjects from the trial/ investigational product treatment.
 - (b) The type and timing of the data to be collected for withdrawn subjects.
 - (c) Whether and how subjects are to be replaced.
 - (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.
- 6.6 *Treatment of Subjects*
- 6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/ mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- 6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- 6.6.3 Procedures for monitoring subject compliance.
- 6.7 *Assessment of Efficacy*
- 6.7.1 Specification of the efficacy parameters.
- 6.7.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.
- 6.8 *Assessment of Safety*
- 6.8.1 Specification of safety parameters.
- 6.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.
- 6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- 6.8.4 The type and duration of the follow-up of subjects after adverse events.
- 6.9 *Statistics*
- 6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- 6.9.2 The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of

sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

- 6.9.3 The level of significance to be used.
- 6.9.4 Criteria for the termination of the trial.
- 6.9.5 Procedure for accounting for missing, unused, and spurious data.
- 6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
- 6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).
- 6.10 *Direct Access to Source Data/Documents*

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/ institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.
- 6.11 *Quality Control and Quality Assurance*
- 6.12 *Ethics*

Description of ethical considerations relating to the trial.

- 6.13 *Data Handling and Recordkeeping*
- 6.14 *Financing and Insurance*

Financing and insurance if not addressed in a separate agreement.
- 6.15 *Publication Policy*

Publication policy, if not addressed in a separate agreement.
- 6.16 *Supplements*

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. *Investigator's Brochure*

7.1 *Introduction*

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/ interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/ her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational

product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRB's)/Independent Ethics Committees (IEC's) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRB's/ IEC's. In the case of an investigator-sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 *General Considerations*

The IB should include:

7.2.1 *Title Page.* This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 *Confidentiality Statement.* The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 *Contents of the Investigator's Brochure.* The IB should contain the following sections, each with literature references where appropriate:

- 7.3.1 *Table of Contents.* An example of the Table of Contents is given in Appendix 2.
- 7.3.2 *Summary.* A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic,

and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction. A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation. A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies.

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested;
- Number and sex of animals in each group;
- Unit dose (e.g., milligram/kilogram (mg/kg));
- Dose interval;
- Route of administration;
- Duration of dosing;
- Information on systemic distribution;
- Duration of post-exposure follow-up;
- Results, including the following aspects:
 - Nature and frequency of pharmacological or toxic effects;
 - Severity or intensity of pharmacological or toxic effects;
 - Time to onset of effects;
 - Reversibility of effects;
 - Duration of effects;
 - Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose

findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose;
- Repeated dose;
- Carcinogenicity;
- Special studies (e.g., irritancy and sensitization);
- Reproductive toxicity;
- Genotoxicity (mutagenicity).

7.3.6 Effects in Humans.

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function).

Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s)).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator.

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on

the pharmacology of the investigational product.

7.4 Appendix 1:

TITLE PAGE OF INVESTIGATOR'S

BROCHURE (Example)

Sponsor's Name:

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 Appendix 2:

TABLE OF CONTENTS OF

INVESTIGATOR'S BROCHURE (Example)

- Confidentiality Statement (optional)

- Signature Page (optional)

1. Table of Contents

2. Summary

3. Introduction

4. Physical, Chemical, and Pharmaceutical Properties and Formulation

5. Nonclinical Studies

5.1 Nonclinical Pharmacology

5.2 Pharmacokinetics and Product

Metabolism in Animals

5.3 Toxicology

6. Effects in Humans

6.1 Pharmacokinetics and Product

Metabolism in Humans

6.2 Safety and Efficacy

6.3 Marketing Experience

7. Summary of Data and Guidance for the Investigator

NB: References on

1. Publications

2. Reports

These references should be found at the end of each chapter.

Appendices (if any)

8. Essential Documents for the Conduct of a Clinical Trial

8.1 Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various

documents are grouped in three sections according to the stage of the trial during which they will normally be generated: (1) Before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.2.1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	Information given to trial subject - Informed consent form (Including all applicable translations) - Any other written information	To document the informed consent	X	X
	- Advertisement for subject recruitment (if used)	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
8.2.4	Financial aspects of the trial	To document that recruitment measures are appropriate and not coercive	X	X
		To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	Signed agreement between involved parties, e.g.: - Investigator/institution and sponsor - Investigator/institution and CRO - Sponsor and CRO - Investigator/institution and authority(ies) (Where required)	To document agreements	X X X X	X X (Where required) X X